# Supplemental Material to:

Ryo Konno, Hiroyuki Yoshikawa, Marie Okutani, Wim Quint, Pemmaraju V Suryakiran, Lan Lin, and Frank Struyf

## Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women: Open follow-up of a randomized clinical trial up to four years post-vaccination

Human Vaccines & Immunotherapeutics 2014;10(7)
http://dx.doi.org/10.4161/hv.28712

www.landesbioscience.com/journals/vaccines/article/28712

**Supplementary Table 1.** Incidence rates and vaccine efficacy against viral infection, cytological, and histological endpoints associated with HPV-16 /18 in women from the TVC-naïve

| | Extended follow-up | | | | | | | Combined study period | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HPV vaccine[a] | | | Control[a] | | | Efficacy (95% CI) | HPV vaccine[a] | | | Control[a] | | | Efficacy (95% CI) |
| | N | Cases | Rate | N | Cases | Rate | | N | Cases | Rate | N | Cases | Rate | |
| Incident infection | | | | | | | | | | | | | | |
| HPV-16/18 | 209 | 5 | 2.95 | 207 | 17 | 11.61 | 74.6% (28.3–92.7) | 263 | 9 | 1.03 | 263 | 42 | 5.29 | 80.5% (59.4–91.7) |
| HPV-16 | 209 | 1 | 0.58 | 207 | 11 | 7.34 | 92.1% (45.3–99.8) | 263 | 6 | 0.69 | 263 | 27 | 3.27 | 79.1% (48.2–92.9) |
| HPV-18 | 209 | 4 | 2.36 | 207 | 7 | 4.58 | 48.5% (−102.5–89.0) | 263 | 6 | 0.68 | 263 | 20 | 2.41 | 71.8% (27.2–90.7) |
| Persistent infection[b] | | | | | | | | | | | | | | |
| HPV-16/18 | 163 | 0 | 0.00 | 148 | 8 | 6.08 | 100% (50.3–100) | 248 | 0 | 0.00 | 245 | 11 | 1.31 | 100% (62.1–100) |
| HPV-16 | 163 | 0 | 0.00 | 148 | 7 | 5.28 | 100% (40.7–100) | 248 | 0 | 0.00 | 245 | 9 | 1.07 | 100% (51.5–100) |
| HPV-18 | 163 | 0 | 0.00 | 148 | 2 | 1.46 | 100% (−370.2–100) | 248 | 0 | 0.00 | 245 | 3 | 0.35 | 100% (−133.3–100) |
| ASC-US+ | | | | | | | | | | | | | | |
| HPV-16/18 | 209 | 1 | 0.58 | 207 | 9 | 5.89 | 90.2% (29.0–99.8) | 254 | 1 | 0.11 | 251 | 16 | 1.91 | 94.1% (61.8–99.9) |
| HPV-16 | 209 | 0 | 0.00 | 207 | 9 | 5.89 | 100% (55.1–100) | 254 | 0 | 0.00 | 251 | 14 | 1.66 | 100% (71.2–100) |
| HPV-18 | 209 | 1 | 0.58 | 207 | 1 | 0.64 | 9.4% (−7011.8–98.9) | 254 | 1 | 0.11 | 251 | 3 | 0.35 | 67.8% (−301–99.4) |
| CIN1+ | | | | | | | | | | | | | | |
| HPV-16/18 | 209 | 0 | 0.00 | 207 | 4 | 2.51 | 100% (−37.9–100) | 254 | 0 | 0.00 | 251 | 8 | 0.94 | 100% (43.6–100) |
| HPV-16 | 209 | 0 | 0.00 | 207 | 4 | 2.51 | 100% (−37.9–100) | 254 | 0 | 0.00 | 251 | 7 | 0.82 | 100% (33.0–100) |
| HPV-18 | 209 | 0 | 0.00 | 207 | 0 | 0.00 | - | 254 | 0 | 0.00 | 251 | 1 | 0.12 | 100% (−3679.1–100) |
| CIN2+ | | | | | | | | | | | | | | |
| HPV-16/18 | 209 | 0 | 0.00 | 207 | 3 | 1.88 | 100% (−120.3–100) | 254 | 0 | 0.00 | 251 | 5 | 0.58 | 100% (−5.4–100) |
| HPV-16 | 209 | 0 | 0.00 | 207 | 3 | 1.88 | 100% (−120.3–100) | 254 | 0 | 0.00 | 251 | 5 | 0.58 | 100% (−5.4–100) |
| HPV-18 | 209 | 0 | 0.00 | 207 | 0 | 0.00 | - | 254 | 0 | 0.00 | 251 | 0 | 0.00 | - |

The left part is based on case counting during the extended follow-up period only; the right part shows data for the combined (initial plus extended) study period; [a]Women were originally vaccinated with either the HPV-16/18 AS04-adjuvanted vaccine (HPV vaccine) or the Hepatitis A vaccine (Control); [b]12-mo definition: women with at least 2 consecutive samples positive for the same HPV type over a minimum of 10 mo; n, number of women included in each group; Cases, number of women reporting at least one event; Rate, incidence rate of women reporting at least on event per year (per 100 women) (cases/follow-up period in years). Abbreviations: ASC-US+, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions; CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; 95% CI, 95% confidence interval (lower limit–upper limit).

**Supplementary Table 2.** Incidence rates and vaccine efficacy against viral infection, cytological, and histological endpoints associated with high-risk HPV types in women from the TVC-naïve

| | Extended follow-up | | | | | | | Combined study period | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HPV vaccine[a] | | | Control[a] | | | Efficacy (95% CI) | HPV vaccine[a] | | | Control[a] | | | Efficacy (95% CI) |
| | N | Cases | Rate | N | Cases | Rate | | N | Cases | Rate | N | Cases | Rate | |
| **Incident infection** | | | | | | | | | | | | | | |
| HPV-31/33/45 | 209 | 3 | 1.77 | 207 | 8 | 5.22 | 66.0% (−41.5–94.2) | 263 | 5 | 0.57 | 263 | 13 | 1.52 | 62.6% (−11.8–89.6) |
| HPV-31/33/45/52/58 | 209 | 26 | 16.21 | 207 | 27 | 18.88 | 14.2% (−52.8–51.9) | 263 | 39 | 4.71 | 263 | 53 | 6.74 | 30.2% (−7.6–55.0) |
| any non-vaccine high-risk type | 209 | 43 | 28.97 | 207 | 47 | 36.03 | 19.6% (−24.2–48.1) | 263 | 67 | 8.68 | 263 | 90 | 12.71 | 31.7% (5.2–51.0) |
| any high-risk type | 209 | 46 | 30.99 | 207 | 53 | 42.41 | 26.9% (−10.6–51.9) | 263 | 71 | 9.32 | 263 | 105 | 15.62 | 40.4% (18.7–56.5) |
| **Persistent infection[b]** | | | | | | | | | | | | | | |
| HPV-31/33/45 | 163 | 0 | 0.00 | 148 | 1 | 0.73 | 100% (−3364.6–100) | 248 | 2 | 0.23 | 245 | 1 | 0.12 | −95.0% (−11403.4–89.9) |
| HPV-31/33/45/52/58 | 163 | 4 | 2.64 | 148 | 8 | 6.10 | 56.7% (−61.6–90.5) | 248 | 10 | 1.16 | 245 | 14 | 1.70 | 31.6 (−65.6–72.8) |
| any non-vaccine high-risk type | 163 | 13 | 9.09 | 148 | 14 | 11.10 | 18.2% (−87.7–64.6) | 248 | 22 | 2.62 | 245 | 28 | 3.52 | 25.5% (−35.0–59.4) |
| any high-risk type | 163 | 13 | 9.09 | 148 | 20 | 16.57 | 45.2% (−15.8–74.9) | 248 | 22 | 2.62 | 245 | 36 | 4.61 | 43.0% (0.5–68.1) |
| **ASC-US+** | | | | | | | | | | | | | | |
| HPV-31/33/45 | 209 | 2 | 1.17 | 207 | 3 | 1.91 | 38.9% (−433.2–94.9) | 254 | 3 | 0.34 | 251 | 3 | 0.35 | 2.5% (−628.2–86.9) |
| HPV-31/33/45/52/58 | 209 | 9 | 5.34 | 207 | 15 | 10.03 | 46.7 (−30.0–79.4) | 254 | 12 | 1.38 | 251 | 22 | 2.63 | 47.6% (−10.5–76.4) |
| any non-vaccine high-risk type | 209 | 16 | 9.65 | 207 | 24 | 16.52 | 41.6% (−14.6–71.0) | 254 | 25 | 2.93 | 251 | 36 | 4.42 | 33.7% (−13.5–61.9) |
| any high-risk type | 209 | 17 | 10.25 | 207 | 28 | 19.58 | 47.6% (0.9–73.1) | 254 | 26 | 3.05 | 251 | 43 | 5.32 | 42.7% (4.6–66.2) |
| **CIN1+** | | | | | | | | | | | | | | |
| HPV-31/33/45 | 209 | 0 | 0.00 | 207 | 2 | 1.25 | 100% (−387.7–100) | 254 | 0 | 0.00 | 251 | 2 | 0.23 | 100% (−417.2–100) |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HPV-31/33/45/52/58 | 209 | 3 | 1.72 | 207 | 5 | 3.14 | 45.1% (−182.2–91.5) | 254 | 5 | 0.57 | 251 | 10 | 1.18 | 51.9% (−54.3–87.1) |
| any non-vaccine high-risk type | 209 | 5 | 2.87 | 207 | 8 | 5.02 | 42.8% (−98.5–85.3) | 254 | 8 | 0.91 | 251 | 14 | 1.65 | 45.1% (−40.3–80.0) |
| any high-risk type | 209 | 5 | 2.87 | 207 | 11 | 6.95 | 58.6% (−29.2–88.7) | 254 | 8 | 0.91 | 251 | 19 | 2.26 | 59.7% (3.6–84.7) |
| | | | | | | | **CIN2+** | | | | | | | |
| HPV-31/33/45 | 209 | 0 | 0.00 | 207 | 0 | 0.00 | - | 254 | 0 | 0.00 | 251 | 0 | 0.00 | - |
| HPV-31/33/45/52/58 | 209 | 0 | 0.00 | 207 | 2 | 1.26 | 100% (−384.9–100) | 254 | 0 | 0.00 | 251 | 5 | 0.59 | 100% (−4.9–100) |
| any non-vaccine high-risk type | 209 | 1 | 0.57 | 207 | 2 | 1.26 | 54.5% (−774.7–99.2) | 254 | 1 | 0.11 | 251 | 5 | 0.59 | 80.8% (−71.8–99.6) |
| any high-risk type | 209 | 1 | 0.57 | 207 | 5 | 3.16 | 81.9% (−61.8–99.6) | 254 | 1 | 0.11 | 251 | 9 | 1.06 | 89.4% (23.2–99.8) |

The left part is based on case counting during the extended follow-up period only; the right part shows data for the combined (initial plus extended) study period; Any high-risk type = high-risk oncogenic HPV types, i.e., HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68; any non-vaccine high-risk type = 12 non-vaccine high-risk oncogenic HPV types, i.e., HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68; [a] Women were originally vaccinated with either the HPV-16/18 AS04-adjuvanted vaccine (HPV) or the Hepatitis A vaccine (Control); [b] 12-mo definition: women with at least 2 consecutive samples positive for the same HPV type over a minimum of 10 mo; n, number of women included in each group; Cases, number of women reporting at least one event; Rate, incidence rate of women reporting at least on event per year (per 100 women) (cases/follow-up period in years). Abbreviations: ASC-US+, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions; CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; 95% CI, 95% confidence interval (lower limit–upper limit).

**Supplementary Table 3.** Safety and pregnancy outcomes (TVC)

| | HPV vaccine (n = 519) | | Control (n = 521) | |
|---|---|---|---|---|
| **A. Safety endpoint** | **n** | **% (95% CI)** | **n** | **% (95% CI)** |
| Serious adverse event (SAE) | 26 | 5.0 (3.3–7.3) | 34 | 6.5 (4.6–9.0) |
| Vaccine-related SAE[a] | 1 | 0.2 (0.0–1.1) | 0 | 0.0 (0.0–0.7) |
| Fatal SAE | 1[b] | 0.2 (0.0–1.1) | 0 | 0.0 (0.0–0.7) |
| Medically significant condition | 98 | 18.9 (15.6–22.5) | 115 | 22.1 (18.6–25.9) |
| New onset chronic disease[c] | 6 | 1.2 (0.4–2.5) | 8 | 1.5 (0.7–3.0) |
| New onset autoimmune disease[c] | 3 | 0.6 (0.1–1.7) | 1 | 0.2 (0.0–1.1) |
| **B. Pregnancy outcomes** | | **n (%)** | | **n (%)** |
| Number of pregnancies | | 83 | | 84 |
| Ongoing pregnancies | | 2 (2.4%) | | 0 |
| Live infant[d] | | 52 (62.7%) | | 53 (63.1%) |
| Live infant with congenital anomaly | | 0 | | 1 (1.2%) |
| Spontaneous abortion[d] | | 8 (9.6%) | | 7 (8.3%) |
| Elective termination[d] | | 18 (21.7%) | | 19 (22.6%) |
| Stillbirth[c] | | 1 (1.2%) | | 0 |
| Ectopic pregnancy | | 0 | | 1 (1.2%) |
| Premature live infant [d] | | 1 (1.2%) | | 0 |
| Lost to follow up | | 1 (1.2%) | | 3 (3.6%) |

n, number of women with at least one administered vaccine dose; n (%), number (percentage) of women reporting at least one event; [a]Participant experienced a spontaneous abortion 15 d after the second dose of HPV vaccine; [b]Participant committed suicide approximately 21 mo after administration of the second dose of the vaccine; [c]New onset chronic diseases and new onset autoimmune diseases presented here were identified by GSK assessment; [d] No apparent congenital anomaly reported.